Creation of analogues of polyketides of interest by genetic engineering and allied approaches

The PhD project will be carried out jointly between two research units of the University of Lorraine (UL) in Nancy (France): UMR UL-CNRS 7365 Molecular Engineering and Articular Physiopathology (IMoPA) and UMR UL-INRA 1128 Genome dynamics and microbial adaption (DynAMic). The position is proposed within the context of a large initiative within the UL entitled 'Biomolecules and the Bioeconomy', involving 16 internationally recognized laboratories as well as local and international companies.

The overall aim of the Biomolecules project is to identify promising bioactive molecules for industrial application. It involves different "workpackages" ranging from microbial interactions to induce biosynthesis of potential compounds of interest, to screening bioactivities against specific targets, to functionalization to improve the potential of promising hits, to formulation/delivery studies (encapsulation and vectorization) to facilitate the transition into industrial application.

The proposed PhD project will focus on polyketide secondary metabolites from bacteria. These types of molecules are a major source of medicines in both human and animal therapy, and thus there is significant interest in obtaining analogues of these structures for evaluation as drug leads. In this context, rational manipulation of the biosynthetic pathways (including the gigantic multienzyme polyketide synthases (PKSs) responsible for the synthesis of the polyketide cores) using synthetic biology represents an attractive and developing approach to generate additional, potentially valuable derivatives.

The project aims to demonstrate proof-of-principle for this idea using a small set of polyketides produced by *Streptomyces* which exhibit promising anti-cancer activities. Two main approaches will initially be developed to generate a panel of derivatives: rational manipulation of interpolypeptide interfaces to change the order of the subunits and precursor-directed biosynthesis/ mutasynthesis. Genetic engineering of the producing strain will also be explored in order to ensure sufficient quantities of compounds for structural analysis and biological testing.

The proposed project, which unites the complementary expertise available in the two participating laboratories, will allow the PhD student to acquire a wide range of skills ranging from *Streptomyces* microbiology to genetic engineering to small molecule analysis. He/she will additionally benefit from additional approaches developed by the consortium (genomics, protein engineering, analytical chemistry, activity screening…).

Keywords: polyketide, polyketide synthase, macrolides, synthetic biology

Please mail your CV, letter of motivation and at least two references simultaneously to Christine Fivet, Ecole Doctorale RPPE, (Christine.fivet@univ-lorraine.fr) to register your application, and to both Kira Weissman (kira.sourmail@univ-lorraine.fr, IMoPA, UMR UL-CNRS 7365) and Bertrand Aigle (bertrand.aigle@univ-lorraine.fr, DynAMic, UMR UL INRA 1128) who are supervising the scientific project. The application deadline application is 30 May 2017. Selected candidates will be invited for an interview around 15 June. The PhD contract will start in September 2017.